Extended Lymphadenectomy and Vein Resection for Pancreatic Head Cancer

Outcomes and Implications for Therapy

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Hypothesis: An aggressive strategy that includes extended lymphadenectomy and vein resection may improve the results of surgical treatment of pancreatic head cancer.

Design: Nonrandomized control trial.

Setting: Tertiary care referral center.

Patients: The study included 149 consecutive patients undergoing macroscopically curative resection for periampullary adenocarcinoma from January 1, 1988, to December 31, 1998.

Interventions: A standard resection was performed in 122 cases; an extended lymphadenectomy in 37. Twenty-four patients underwent venous resection.

Main Outcome Measures: Data on surgical mortality, morbidity, and postoperative outcome, pathological findings, and long-term survival were analyzed.

Results: In-hospital and 60-day operative mortality was 5.4%. Morbidity was 37.5%. Mortality, morbidity, and postoperative stay were nonsignificantly modified by extended lymphadenectomy or venous resection. Extended resection permitted the identification of a significantly higher percentage of nodal metastases beyond the peripancreatic node groups. In patients undergoing vein resection, a significantly higher rate of positive retroperitoneal margin was found. In the 100 patients with ductal adenocarcinoma, the median overall survival and the 5-year actuarial survival rate were 15 months and 8.4%, respectively. A trend toward a better survival was observed in the first 2 years after operation in the extended resection group compared with the standard resection group. Nodal status was the most powerful predictor of overall survival by multivariate analysis.

Conclusions: Extended lymphadenectomy and vein resection did not adversely affect postoperative mortality and morbidity. Patients who required a vein resection were less likely to receive a microscopically curative pancreatectomy. Extended resection permitted better pathological staging and was associated with an early advantage in survival, but long-term survival was possible only in patients with favorable prognostic factors.

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PATIENT METHODS

PATIENT POPULATION

All patients undergoing macroscopically curative resection for peripancreatic adenocarcinoma at Ospedale Mauriziano Umberto I, Torino, Italy, from January 1, 1988, to December 31, 1998, excluding cystic or intraductal papillary tumors, were considered for the analysis of early postoperative results. Patients with a final diagnosis of ductal adenocarcinoma were considered for the analysis of pathological data and survival.

PREOPERATIVE EVALUATION

Abdominal ultrasonography followed by contrast computed tomography were performed in all the cases. Distant metastases, celiac trunk (CT) or superior mesenteric artery (SMA) encasement, or thrombosis of the portal vein (PV) and/or the superior mesenteric vein (SMV) were considered contraindication for operation. Preoperative bile duct drainage was accomplished endoscopically only in the case of bile duct infection or when a period of parenteral nutrition was needed before surgery.

SURGICAL TECHNIQUE

After examination of the abdominal cavity, inspection and palpation of the liver, and estimation of the local extent of the primary tumor, patients with distant metastases or involvement of the SMV beyond the transverse mesocolon underwent a bypass operation. All other patients were considered eligible for surgical resection. The resection was accomplished by a standard Whipple procedure or by a pylorus-preserving pancreatoduodenectomy (PPPD), according to the site of the tumor and its distance from the pylorus. Bile duct and pancreatic neck margins were checked by frozen section before performing the anastomosis. In case of positivity, an additional resection was performed until a negative margin was obtained. If it was impossible to perform an additional resection on the pancreatic side, a total pancreatectomy was performed. Moreover, a total pancreatectomy was performed in patients with local complications from obstructive chronic pancreatitis and who were already insulin dependent before surgery.

Since 1994, on the basis of the reports from Japan, all the patients who consented and in whom a ductal adenocarcinoma was identified by an extemporary analysis of the specimen were offered an extended lymphadenectomy. We decided to perform the extended operation when a ductal adenocarcinoma was identified during the operation because of its worse prognosis and higher nodal positivity rate compared with the other peripancreatic neoplasms. In addition to the nodal groups resected with the standard procedure (eg, anterior and posterior pancreaticoduodenal nodes, nodes in the lower hepatoduodenal ligament, and nodes along the right lateral aspect of the SMA), the extended resection included a retroperitoneal lymphatic dissection that extended, in the vertical axis, from the CT to the inferior mesenteric artery and, in the transverse plane, from the right border of the vena cava to the left border of the aorta. The hepatic pedicle, the common hepatic artery, the CT, the SMA on its anterior and right lateral aspects, and the anterior aspect of the vena cava and the aorta between the boundaries defined herein were skeletonized (Figure). During a PPPD, inferior pyloric nodes were removed separately.

Throughout the study period, when an indissociable adhesion of the tumor to the PV or SMV was encountered after transection of the pancreatic neck, a venous resection was performed. In addition, a segmental vein resection was performed whenever the detachment of the specimen from the vein wall was possible but a neoplastic venous invasion was strongly suspected because a rigid or thickened vein wall was left behind. No attempt was made to detect the neoplastic involvement of the vein by intraoperative frozen section.

PATHOLOGICAL EXAMINATION

Tumors were classified by site and grade according to World Health Organization criteria. Pathological stage was assessed according to the Union Internationale Contre le Cancer TNM system. All the resected veins were checked for direct invasion by the tumor. Pancreatic neck, bile duct, jejunal, duodenal, or gastric margins were studied on definitive sections. Since 1996, the retroperitoneal surface and uncinate margins, marked by the surgeon at the time of resection, were studied by serial sections after coloration with India ink. When an extended resection was performed, the tissue, even when removed en bloc, was sent to the pathologist after division of lymph node groups from the specimen. The nomenclature proposed by the Japanese Pancreas Society was followed (Table 1). Lymphatic groups were analyzed separately for number of nodes collected and number of nodes involved in the tumor. Node groups were sorted into 3 groups: peripancreatic, regional, and distant (Table 1).

DATA COLLECTION AND STATISTICAL ANALYSIS

Clinical and pathological data were extracted from a prospectively maintained database. To define the impact of extended lymphadenectomy or vein resection on the postoperative course of pancreatoduodenectomy, all peripancreatic tumors were included in the analysis of short-term outcome. Patients who did or did not undergo an extended lymphadenectomy or a vein resection were compared for operative time, need for blood transfusions, in-hospital and 60-day operative mortality, postoperative complications, and length of hospital stay. Continuous variables were reported as mean ± SD and compared by the t test (2-tailed, unpaired). Categoric variables were compared by the χ² test or Fisher exact test, as appropriate. P<.05 was considered statistically significant for all tests.
The analysis of pathological data and long-term outcome was performed on patients with a final diagnosis of ductal adenocarcinoma. Postoperative follow-up was performed by outpatient clinics or by contacting the general practitioner of the patients and was updated to August 2002. Survival was computed from the date of operation. Patients lost to follow-up were censored at the time of last contact. The univariate analysis of survival was performed comparing clinical and pathological factors by the log-rank test. Clinical variables included sex, age (cutoff at 65 years), preoperative biliary drainage, operation type (Whipple procedure vs total pancreatectomy, including completion pancreatectomy, and Whipple procedure vs PPPD), type of lymphadenectomy, vein resection, and blood transfusion. Pathological data included tumor grading (G1-2 vs G3), tumor diameter (cutoff at 2 cm), invasion of peripancreatic soft tissues, vascular wall invasion in case of vein resection, presence and level of nodal metastases (peripancreatic vs regional vs distant), surgical margins status, perineural invasion, and presence of neoplastic emboli. The multivariate analysis was performed, including all the significant (P<.05) and borderline significant (P<.10) factors on univariate analysis, using a Cox regression model.

**STUDY POPULATION AND PROCEDURES**

From January 1, 1988, to December 31, 1998, 149 patients with peripancreatic adenocarcinoma underwent a macroscopically curative resection. The site at final pathological examination was the pancreatic duct in 100 cases, the bile duct in 12, the duodenum in 5, the papilla of Vater in 22, and unspecified in 10. There were 56 women and 93 men. Mean age at surgery was 63.5±9.8 years (range, 29-81 years). Forty-two patients (28%) had a biliary drain in place at the time of operation. Twenty-eight patients were referred with a biliary stent; 14 underwent an endoscopic bile duct drainage at our institution. A pancreatic head resection was performed in 132 cases (89%) and a total pancreatectomy in 17 (11%). The pylorus was preserved in 48 patients. Since 1994, an extended lymphadenectomy was performed in 37 cases; 32 were ductal adenocarcinomas. During the same period, only 5 patients with ductal cancer refused the extended operation and were treated by standard resection. A venous resection was required in 24 cases (16%); 22 were ductal cancers. The PV was resected in 4 cases, the SMV in 11, and the mesenteric-portal confluence in 9, with reimplantation of the splenic vein in 3 cases. In all the cases, a direct reconstruction without graft interposition was possible. Seven patients underwent vein resection during an extended lymphadenectomy.

**SHORT-TERM RESULTS**

The postoperative course was uneventful in 93 patients. In-hospital and 60-day operative mortality was 5.4%. Morbidity was 37.5%. An additional operation was required in 21 cases. In 8 cases, a completion pancreatectomy was performed. Mortality and morbidity rates were not significantly different when an extended lymphadenectomy or a venous resection was performed. The 7 patients who underwent an extended lymphadenectomy with vein resection did not experience any complications. Causes of death, complications, and their relative incidences according to type of lymphadenectomy and vein resections are detailed in Table 2 and Table 3.

We did not observe bowel function alteration after extended lymphadenectomy compared with the standard Whipple procedure. Blood transfusion was required in 74 patients (50%). The mean and median numbers of blood units transfused were 1.2±1.5 and 0, respectively. Data for blood transfusions, operative time, and postoperative stay relative to extended lymphadenectomy and vein resection are given in Table 4.

**PATHOLOGICAL FINDINGS**

Data were available for 100 patients with a final diagnosis of ductal adenocarcinoma, including 22 patients who underwent a vein resection and 32 patients who underwent an extended lymphadenectomy. Mean tumor diameter was 3.7±1.3 cm. Twenty patients had a tumor diameter of 2 cm or less. Direct invasion of extrapancreatic retroperitoneal soft tissues was found in 31 cases. Vein wall invasion was found in 18 (82%) of 22 patients who underwent vein resection. The extended lymphadenectomy yielded a mean of 32.4±12.3 nodes. This figure was significantly higher percentage of regional metastases was identified compared with standard resection (P<.001). Nodal metastases were identified in 59 patients. In detail, among 68 patients who underwent a standard procedure, 31 (46%) were node negative, 24 (35%) had nodal metastases confined to peripancreatic areas, and 13 (19%) had both peripancreatic and regional nodal metastases. Among 32 patients who underwent an extended lymphadenectomy, 10 (31%) were node negative, 10 (31%) had only peripancreatic metastases, and 12 (37%) had also regional metastases. A significantly higher percentage of regional metastases was identified compared with standard resection (P=.048).

According to the Japanese Pancreas Society classifications, the involvement rate for peripancreatic nodes was 59% in the No. 13/17 group, 0% in the No. 5 group, 12% in the No. 6 group, and 3% in the No. 12 group. For regional nodes, there were 6% in the No. 8 group, 9% in the No. 9 group, 22% in the No. 14 group, and 3% in the No. 15 group. In addition, extended lymphadenectomy...
disclosed clinically inapparent metastases to preaortic lymph nodes in 8 patients (25%). Neoplastic emboli and perineural invasion were documented in 55 and 72 patients, respectively. The final Union Internationale Contre le Cancer stage was I in 11 cases, IIA in 30, IIB in 51, and IV in 8 for the presence of distant lymph node metastases. Duodenal, gastric, jejunal, or biliary margins were always found free of tumoral involvement. The pancreatic neck margin was positive for cancer on the frozen section analysis in 12 cases. A margin negative for cancer was obtained by an additional neck resection in 2 patients and a total pancreatectomy in 10. In another 2 cases judged negative for cancer by frozen analysis, a positive neck margin was identified on definitive sections. One of these patients underwent a completion pancreatectomy, whereas the other one refused an additional operation. The retroperitoneal margin was analyzed in 30 patients and was positive for cancer in 10 (33%). A comparison of pathological factors among patients with or without vein resection was performed (Table 5). Patients who required a vein resection were more likely to have a positive retroperitoneal margin.

LONG-TERM RESULTS

At the end of the follow-up period, 6 patients were alive and free of disease, with a minimum and mean follow-up of 43 and 106 months, respectively. Five patients were lost to follow-up after a mean of 3 months after the operation. All the other 81 patients who survived the operation died of recurrence. Median overall survival was 15 months. Overall 1-, 3-, and 5-year actuarial survival rates were 68.5%,

Table 2. Short-term Morbidity Results*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Extended Lymphadenectomy</th>
<th>Vein Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 37)</td>
<td>No (n = 112)</td>
</tr>
<tr>
<td>Pancreatic fistula (excluding total pancreatectomy)</td>
<td>23/132 (17)</td>
<td>18/98 (18)</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>11 (7)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Intra-abdominal hemorrhage</td>
<td>7 (5)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>5 (3)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (3)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>4 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>4 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Gastroenteric leak</td>
<td>3 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Small-bowel obstruction</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Biliary leak</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Overall morbidity</td>
<td>56 (37.5)</td>
<td>43 (38.3)</td>
</tr>
<tr>
<td>Additional operations</td>
<td>21 (14.5)</td>
<td>17 (15.2)</td>
</tr>
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</table>

Table 3. Short-term Mortality Results*

<table>
<thead>
<tr>
<th>Result</th>
<th>Extended Lymphadenectomy</th>
<th>Vein Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 37)</td>
<td>No (n = 112)</td>
</tr>
<tr>
<td>Major arrhythmia</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hemoperitoneum</td>
<td>2 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pancreatic fistula related</td>
<td>4 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>8 (5.4)</td>
<td>6 (3.3)</td>
</tr>
</tbody>
</table>

Table 4. In-Hospital Outcome Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vein Resection</th>
<th>Extended Lymphadenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time, mean ± SD, h</td>
<td>6.3 ± 1.2</td>
<td>5.6 ± 1.3</td>
</tr>
<tr>
<td>Blood transfusion, mean ± SD (median), U</td>
<td>2.1 ± 1.9 (2)</td>
<td>1.0 ± 1.4 (0)</td>
</tr>
<tr>
<td>Length of stay, mean ± SD (median), d</td>
<td>25.5 ± 16.6 (20.5)</td>
<td>20.7 ± 14.3 (17)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients.
16.3%, and 8.4%, respectively. Extended lymphadenectomy and vein resection did not result in significant prognostic factors at univariate analysis. The multivariate analysis of overall survival is displayed in Table 6. Long-term survival was not observed in the presence of nodal metastases, vein wall invasion, neoplastic emboli, or positive retroperitoneal margin. The longest survival times observed according to node-level involvement were 57, 37, and 23 months for patients with positive peripancreatic, regional, and distant nodes, respectively. Excluding postoperative deaths, a trend toward a better survival after extended resection was observed in the first 2 years after the operation compared with standard resection. The 12-month survival rates after standard resection for the entire group, the node-positive patients, and the node-negative patients were 64.6%, 57.6%, and 72.4%, respectively. The same figures were 76.7% (P = .07), 66.7% (P = .09), and 100% (P = .17), respectively, after extended resection. A multivariate analysis was performed to identify the predictors of survival in the first 2 years after operation. Extended lymphadenectomy resulted in an independent prognostic factor (Table 7). Patients undergoing extended or standard resection were matched for all the clinical and pathological factors considered for the univariate analysis of survival. The 2 groups were comparable for all but sex, grading, and blood transfusion. Table 8 displays partially this comparison, reporting the mismatching factors in addition to those positive by univariate analysis.

**COMMENT**

The first attempt to improve the results of pancreatic cancer therapy by a more aggressive surgical strategy was reported in 1973 by Fortner with the regional pancreatectomy. This demanding operation, which is no longer used, included 2 main components: a wide peripancreatic soft tissue clearance and a systematic resection of major peripancreatic vascular structures. During the past few decades, the issues of extended lymphadenectomy and vein resection have been investigated separately in several studies, with conflicting conclusions. Data from these studies are difficult to compare because of wide differences regarding patient selection, surgical technique, and associated treatments.

In the late 1980s, the wide retroperitoneal clearance performed in Japan yielded an apparent increase in 5-year survival rates. However, an extensive multi-institutional review of 1001 patients who underwent operations at 77 medical facilities did not confirm these results. Moreover, the Eastern-type operation has been associated with a high incidence of postoperative watery diarrhea, malnutrition, and the need for late readmissions. The Western-type lymphadenectomy is less ex-
tensive and includes, to different extents, the removal of lymph nodes from the hepatic hilum and along the aorta and caval anterior surface with clearance of the origin of the CT and SMA. The first prospective, randomized trial that addressed this issue included 81 patients with pancreatic head ductal cancer and was published in 1998 by Pedrazzoli et al. Their lymphadenectomy field was extended from the diaphragm to the inferior mesenteric artery, with complete skeletonization of the CT, SMA, and hepatic pedicle. It retrieved a mean of 20 nodes, compared with 13 nodes for the standard resection, and did not affect postoperative mortality or morbidity. These investigators did not find any improvement in survival at final analysis. However, by a post hoc analysis, similar to what had been previously reported by Gall et al. in a retrospective study, they found a survival advantage for lymphadenectomy in the subgroup of node-positive patients. A prospective, nonrandomized trial on a group of 72 patients with ductal head cancer was published in 2000 by Henne-Bruns et al. The extended resection harvested a mean of 24 nodes (compared with 14 for standard resection) and was associated with a high incidence of watery diarrhea related to the circumferential clearance of the SMA. The largest randomized controlled trial comes from The Johns Hopkins University in Baltimore, Md. The short-term and early long-term results were published recently by Yeo et al. In this trial, 294 patients with periampullary adenocarcinoma were allocated to extended lymphadenectomy with distal gastrectomy vs standard PPPD. During the extended operation, the SMA was cleared along its right and anterior aspect, whereas the CT was only sampled. It harvested a mean of 27 nodes, compared with 16 for the standard PPPD, and was accomplished with the same mortality and slightly increased morbidity, which was mainly due to the associated antrectomy. With a mean follow-up of 24 months, there was no evidence of any advantage on survival by extended resection.

Our lymphadenectomy field extension is in between the techniques described herein. Similar to the approach used by Pedrazzoli and colleagues, we remove hepatic pedicle and CT node basins, but, similar to the approach of Yeo and coauthors, we preserve the nerve plexus on the left aspect of the SMA. In our experience, this was enough to avoid postoperative watery diarrhea. Our data confirm that the Western-type extended operation should yield a mean of 30 nodes. In our hands, extended lymphadenectomy did not affect mortality and morbidity, even if these figures were higher than our previously reported mortality and morbidity rates after pancreaticoduodenectomy for chronic pancreatitis. Moreover, it did not significantly increase operative time or postoperative stay. The need for less blood is due to the fact that extended operations were concentrated in the more recent part of our experience. The extended lymphatic clearance disclosed a 2-fold percentage of regional nodal involvement compared with standard resection (37% vs 19%) and identified distant nodal metastases in 25% of cases. Nobody among the latter group of patients was alive 24 months after the operation. Therefore, the extended lymphatic dissection permits better pathological staging, disclosing more frequent involvement of regional and distant node stations and identifying patients with a worse prognosis who could benefit from adjuvant therapy.

Our findings concerning survival after extended resection are difficult to interpret. In our experience, the extended resection seems to offer an early advantage on survival in both node-positive and node-negative patients. In fact, it had no influence on long-term survival but was the most powerful determinant of 2-year survival by multivariate analysis. These data, obtained by a nonrandomized comparison of nonconcurrent groups, may result from study biases and must be considered with caution. However, the 2 groups seem comparable for clinic and pathological factors. Significant differences were observed only for sex, blood transfusion, and grading. Female sex has been rarely reported as a positive prognostic factor. Blood transfusion has been associated with a worse outcome in several series. For us, these 2 factors did not significantly affect survival by the univariate analysis. Grading was a significant predictor of survival by univariate analysis, but it should have favored the standard resection group. Therefore, we think that the finding of a shift toward a better survival in the early follow-up period, although not reliable enough to draw any conclusions, is worth consideration. In fact, it is similar to the findings observed when radiotherapy is associated with a macroscopically curative resection and could be interpreted as expression of better local disease control. The latter may be an interesting hypothesis to test in future trials.

The other original idea of the operation planned by Fortner was the vascular resection. It is currently generally accepted that the isolated involvement of the portal or mesenteric vein should not be a contraindication to resection. Two large series that compared pancreaticoduodenectomy with or without vein resection were published in 1996 from MD Anderson Cancer Center in Houston, Tex., and Memorial Sloan-Kettering Cancer Center in New York, NY. In both series, the vein resection was proved to be safe and did not affect mortality and morbidity even if it caused a significant increase of blood transfusions (1 vs 3 U in both series). These findings are confirmed in our series; vein resections significantly increased operative time and blood need but did not affect mortality, morbidity, and postoperative stay.

Previous studies reported that vein resection per se did not affect long-term survival. Three of 11 long-term survivors described by Harrison et al. underwent a vein resection. On the other hand, the invasion of the vein wall was a negative prognostic factor in several series. Some investigators were able to find a correlation between the depth of parietal invasion and survival. Because the parietal invasion cannot be reliably predicted by imaging techniques currently available and cannot be definitively assessed even during operation, we believe that tumors that lack a clear fat plane with the venous axis on CT scan or without a clear cleavage plane with the venous wall during dissection should not be excluded from surgery. Otherwise, some patients with mere adherence to a vein or with minimal wall invasion will lose a chance for cure.

The percentage of veins resections reported ranges from 5% to 80% according to the different indications to resection in each institution and is higher in the Eastern
In conclusion, an aggressive surgical attitude toward periampullary soft and vascular tissues does not affect postoperative mortality and morbidity and does not improve long-term survival after resection for pancreatic head cancer. Surgery alone provides long-term survival to only a small percentage of patients with favorable prognostic factors. Nevertheless, extended lymphadenectomy seems to be associated with an early advantage on survival and provides a more precise pathological staging for identifying subgroups with different prognoses. This information can be useful to select adjuvant therapies and to compare different treatment regimens. On the contrary, patients who need a vein resection are less likely to receive a microscopically curative operation. This finding suggests that patients in whom a vein resection can be predicted on the basis of preoperative radiologic assessment could be good candidates for preoperative chemoradiation regimens to improve the surgical cure rate. We hope that better survival results will be obtained with a multimodality approach in which surgery is only a part of a more complex therapeutic strategy. The present data set will offer a basis for comparison to our protocols, including chemotherapy and radiotherapy, currently under way.

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REFERENCES